

Attorney Docket No. 3806-0510-00
Application No.: 09/909,797

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions and listings of claims in the application:

1. (Previously Presented): A composition comprising at least one salt chosen from alkali and alkaline-earth metal salts of at least one sulphated polysaccharide of heparin, said salts of at least one sulphated polysaccharide of heparin comprising:
 - a mean molecular weight in the range of 1500 to 3000 daltons;
 - an anti-Xa activity in the range of 110 to 150 IU/mg;
 - an anti-IIa activity in the range of up to 10 IU/mg; and
 - an anti-Xa activity/anti-IIa activity ratio greater than 10:1.
2. (Previously Presented): A composition comprising at least one salt chosen from alkali and alkaline-earth metal salts of at least one sulphated polysaccharide of heparin, in which said salts of at least one sulphated polysaccharide of heparin have 2 to 26 saccharide units, have an anti-Xa activity in the range of 110 to 150 IU/mg, have a mean molecular weight in the range of 1500 to 3000 daltons, and have a 4,5-unsaturated glucuronic acid 2-O-sulphate unit on at least one end.

3 and 4. (Cancelled)

Attorney Docket No. 3806-0510-00
Application No.: 09/909,797

5. (Previously Presented) A composition according to claim 1 having a mean molecular weight in the range of 2000 to 3000 daltons.
6. (Previously Presented) A composition according to claim 1 having anti-Xa activity in the range of 140 to 150 IU/mg and a mean molecular weight in the range of 2000 to 3000 daltons.
7. (Previously Presented) A composition according to claim 1, in which said salts are chosen from sodium, potassium, calcium, and magnesium salts.
8. (Previously Presented) A composition according to claim 1, having an anti-IIa activity up to 5 IU/mg.
9. (Original) A composition according to claim 1, having an anti-Xa activity:anti-IIa activity ratio greater than 25.
10. (Previously Presented) A method of preparing at least one salt chosen from alkali and alkaline-earth metal salts of at least one sulphated polysaccharide of heparin comprising:
depolymerizing at least one quarternary ammonium salt of the benzyl ester of heparin in an organic medium with at least one phosphazene base;

Attorney Docket No. 3806-0510-00
Application No.: 09/909,797

converting the at least one quarternary ammonium salt of the benzyl ester of the depolymerized heparin to at least one salt chosen from alkali and alkaline-earth metal salts of at least one sulphated polysaccharide of heparin;
saponifying the at least one salt; and
optionally purifying the at least one salt.

11. (Previously Presented) The method according to claim 10, in which said salts of at least one sulphated polysaccharide of heparin have a mean molecular weight in the range of 1500 to 3000 daltons.

12. (Previously Presented) The method according to claim 10, in which said salts of at least one sulphated polysaccharide of heparin have an anti-Xa activity in the range of 94 to 150 IU/mg.

13. (Previously Presented) The method according to claim 10, in which said salts of at least one sulphated polysaccharide of heparin have an anti-IIa activity up to 10 IU/mg.

14. (Previously Presented) The method according to claim 10, in which said salts of at least one sulphated polysaccharide of heparin have an anti-Xa activity:anti-IIa activity ratio greater than 10:1.

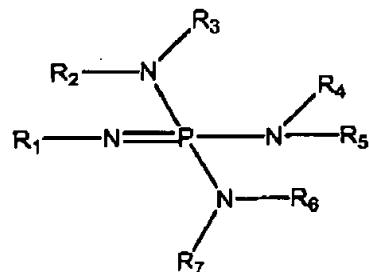
Attorney Docket No. 3806-0510-00
Application No.: 09/909,797

15. (Previously Presented) The method according to claim 10, in which said salts of at least one sulphated polysaccharide of heparin have 2 to 26 saccharide units and have a 4,5-unsaturated glucuronic acid 2-O-sulphate unit on at least one end.

16. (Previously Presented) The method according to claim 10, in which the quarternary ammonium salt of the benzyl ester of heparin is chosen from benzethonium, cetylpyridinium, and cetyltrimethylammonium salts.

17-19. (Cancelled)

20. (Previously Presented) The method according to claim 10, in which the at least one phosphazene base is chosen from:



where R₁ to R₇ are identical or different, and are each chosen from C₁-C₆ alkyl.

21. (Previously Presented) The method according to claim 10, in which the mol ratio of the at least one phosphazene base to the at least one quarternary ammonium salt of the benzyl ester of heparin ranges from 0.2:1 to 5:1.

Attorney Docket No. 3806-0510-00
Application No.: 09/909,797

22. (Previously Presented) The method according to claim 10, in which said at least one quarternary ammonium salt of the benzyl ester of heparin has a degree of esterification ranging from 50 to 100%.

23. (Previously Presented) The method according to claim 10, in which the at least one quarternary ammonium salt of the benzyl ester of depolymerized heparin is converted to a sodium salt by treating the reaction medium with an alcoholic solution of sodium acetate.

24. (Original) The method according to claim 10, in which the saponification is carried out by an alkali metal hydroxide.

25. (Original) The method according to claim 10, in which the purification is carried out by hydrogen peroxide.

26. (Previously Presented) A method of preparing at least one salt chosen from alkali and alkaline-earth metal salts of at least one sulphated polysaccharide of heparin comprising:

depolymerizing at least one quarternary ammonium salt of the benzyl ester of heparin in an organic medium with sodium imidazolate;

converting the at least one quarternary ammonium salt of the benzyl ester of the depolymerized heparin to at least one salt chosen from alkali and alkaline-earth metal salts of at least one sulphated polysaccharide of heparin;

Attorney Docket No. 3806-0510-00
Application No.: 09/909,797

saponifying the at least one salt; and
optionally purifying the at least one salt.

27. (Previously Presented) The method according to claim 26, in which said salts of at least one sulphated polysaccharide of heparin have a mean molecular weight in the range from 1500 to 3000 daltons.

28. (Previously Presented) The method according to claim 26, in which said salts of at least one sulphated polysaccharide of heparin have an anti-Xa activity in the range from 94 to 150 IU/mg.

29. (Previously Presented) The method according to claim 26, in which said salts of at least one sulphated polysaccharide of heparin have an anti-IIa activity up to 10 IU/mg.

30. (Previously Presented) The method according to claim 26, in which said salts of at least one sulphated polysaccharide of heparin have an anti-Xa activity:anti-IIa activity ratio greater than 10:1.

31. (Previously Presented) The method according to claim 26, in which said salts of at least one sulphated polysaccharide of heparin have 2 to 26 saccharide units and have a 4,5-unsaturated glucuronic acid 2-O-sulphate unit on at least one end.

Attorney Docket No. 3806-0510-00
Application No.: 09/909,797

32. (Previously Presented) The method according to claim 26, in which the at least one quarternary ammonium salt of the benzyl ester of heparin is chosen from benzethonium, cetylpyridinium, and cetyltrimethylammonium salts.

33. (Previously Presented) The method according to claim 26, in which the mol ratio of the sodium imidazolate to the at least one quarternary ammonium salt of the benzyl ester of heparin ranges from 0.2:1 to 5:1.

34. (Previously Presented) The method according to claim 26, in which said at least one quarternary ammonium salt of the benzyl ester of heparin has a degree of esterification ranging from 50 to 100%.

35. (Previously Presented) The method according to claim 26, in which the at least one quarternary ammonium salt of the benzyl ester of depolymerized heparin is converted to a sodium salt by treating the reaction medium with an alcoholic solution of sodium acetate.

36. (Original) The method according to claim 26, in which the saponification is carried out by an alkali metal hydroxide.

37. (Original) The method according to claim 26, in which the purification is carried out by hydrogen peroxide.

Attorney Docket No. 3806-0510-00
Application No.: 09/909,797

38. (Previously Presented) A method of treating venous thrombosis in a patient in need of such treatment, comprising administering to the patient a composition as claimed in claim 2, in an amount efficacious for the treatment of venous thrombosis.

39. (Previously Presented) A method of treating venous thrombosis in a patient in need of such treatment, comprising administering to the patient a composition as claimed in claim 1, in an amount efficacious for the treatment of venous thrombosis.

40. (Previously Presented) A method of treating venous thrombosis in a patient in need of such treatment, comprising administering to the patient a composition as claimed in claim 57, in an amount efficacious for the treatment of venous thrombosis.

41. (Previously Presented) A method of treating arterial thrombosis in a patient in need of such treatment, comprising administering to the patient a composition as claimed in claim 2, in an amount efficacious for the treatment of arterial thrombosis.

42. (Previously Presented) A method of treating arterial thrombosis in a patient in need of such treatment, comprising administering to the patient a composition as claimed in claim 1, in an amount efficacious for the treatment of arterial thrombosis.

43. (Previously Presented) A method of treating arterial thrombosis in a patient in need of such treatment, comprising administering to the patient a composition as claimed in claim 57, in an amount efficacious for the treatment of arterial thrombosis.

Attorney Docket No. 3806-0510-00
Application No.: 09/909,797

44. (Previously Presented) A method of treating arterial or venous thrombosis in a patient in need of such treatment comprising the administration of a solution of a pharmaceutical composition by the subcutaneous, intramuscular, intravenous, or pulmonary route, in which a composition according to claim 2 is an active ingredient present in an amount efficacious for such treatment.

45. (Previously Presented) A method of treating arterial or venous thrombosis in a patient in need of such treatment comprising the administration of a solution of a pharmaceutical composition by the subcutaneous, intramuscular, intravenous, or pulmonary route, in which a composition according to claim 1 is an active ingredient present in an amount efficacious for such treatment.

46. (Previously Presented) A method of treating arterial or venous thrombosis in a patient in need of such treatment comprising the administration of a solution of a pharmaceutical composition by the subcutaneous, intramuscular, intravenous, or pulmonary route, in which a composition according to claim 57 is an active ingredient present in an amount efficacious for such treatment.

47-55. (Cancelled)

Attorney Docket No. 3806-0510-00
Application No.: 09/909,797

56. (Previously Presented) A composition comprising at least one salt chosen from alkali and alkaline-earth metal salts of at least one sulphated polysaccharide of heparin, wherein said salt is prepared according to the method of claim 10.

57. (Previously Presented) A composition according to claim 2 having anti-Xa activity in the range of 125-150 IU/mg.

58. (Previously Presented) A composition according to claim 1, in which said at least one salt is sodium salt.

59. (Previously Presented) A method of preparing at least one salt chosen from alkali and alkaline-earth metal salts of at least one sulphated polysaccharide of heparin comprising:

depolymerizing at least one quarternary ammonium salt of the benzyl ester of heparin in an organic medium with 1,5,7 triazabicyclo-[4.4.0]-dec-5-ene;

converting the at least one quarternary ammonium salt of the benzyl ester of the depolymerized heparin to at least one salt chosen from alkali and alkaline-earth metal salts of at least one sulphated polysaccharide of heparin;

saponifying the at least one salt; and

optionally purifying the at least one salt.

Attorney Docket No. 3806-0510-00
Application No.: 09/909,797

60. (Previously Presented) The method according to claim 10, wherein said at least one phosphazene base is 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diaza-phosphorine.

61. (Previously Presented) A method of preparing at least one salt chosen from alkali and alkaline-earth metal salts of at least one sulphated polysaccharide of heparin comprising:

depolymerizing at least one quarternary ammonium salt of the benzyl ester of heparin in an organic medium with at least one guanidine base;

converting the at least one quarternary ammonium salt of the benzyl ester of the depolymerized heparin to at least one salt chosen from alkali and alkaline-earth metal salts of at least one sulphated polysaccharide of heparin;

saponifying the at least one salt; and

optionally purifying the at least one salt.

62. (Previously Presented) A method of preparing a composition comprising the sodium salt of at least one sulphated polysaccharide of heparin, said sodium salt of at least one sulphated polysaccharide of heparin comprising:

a mean molecular weight in the range of 1500 to 3000 daltons;

an anti-Xa activity in the range of 94 to 150 IU/mg;

an anti-IIa activity in the range of up to 10 IU/mg; and

an anti-Xa activity/anti-IIa activity ratio greater than 10:1

Attorney Docket No. 3806-0510-00
Application No.: 09/909,797

wherein said method comprises:

depolymerizing a quaternary ammonium salt of the benzyl ester of heparin in an organic medium with a phosphazene base;

converting the quaternary ammonium salt of the benzyl ester of the depolymerized heparin to a sodium salt of at least one sulphated polysaccharide of heparin;

saponifying the sodium salt; and

optionally purifying the sodium salt.

63. (Previously Presented) The method according to claim 62, in which said sodium salt of at least one sulphated polysaccharide of heparin have an anti-Xa activity in the range of 110 to 150 IU/mg.

64. (Previously Presented) A method of preparing a composition comprising the sodium salt of at least one sulphated polysaccharide of heparin, said sodium salt of at least one sulphated polysaccharide of heparin comprising:

a mean molecular weight in the range of 1500 to 3000 daltons;

an anti-Xa activity in the range of 94 to 150 IU/mg;

an anti-IIa activity in the range of up to 10 IU/mg; and

an anti-Xa activity/anti-IIa activity ratio greater than 10:1

wherein said method comprises:

Attorney Docket No. 3806-0510-00
Application No.: 09/909,797

depolymerizing a quaternary ammonium salt of the benzyl ester of heparin in an organic medium with 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diaza-phosphorine;

converting the quaternary ammonium salt of the benzyl ester of the depolymerized heparin to a sodium salt of at least one sulphated polysaccharide of heparin;

saponifying the sodium salt; and

optionally purifying the sodium salt.

65. (Previously Presented) A method of preparing a composition comprising the sodium salt of at least one sulphated polysaccharide of heparin, said sodium salt of at least one sulphated polysaccharide of heparin comprising:

a mean molecular weight in the range of 1500 to 3000 daltons;

an anti-Xa activity in the range of 94 to 150 IU/mg;

an anti-IIa activity in the range of up to 10 IU/mg; and

an anti-Xa activity/anti-IIa activity ratio greater than 10:1

wherein said method comprises:

depolymerizing a quaternary ammonium salt of the benzyl ester of heparin in an organic medium with 1,5,7 triazabicyclo-[4.4.0]-dec-5-ene;

converting the quaternary ammonium salt of the benzyl ester of the depolymerized heparin to a sodium salt of at least one sulphated polysaccharide of heparin;

Attorney Docket No. 3806-0510-00
Application No.: 09/909,797

saponifying the sodium salt; and
optionally purifying the sodium salt.

66. (Previously Presented) A method of preparing at least one salt chosen from alkali and alkaline-earth metal salts of sulphated polysaccharides of heparin comprising:
depolymerizing at least one quarternary ammonium salt of the benzyl ester of heparin in an organic medium with at least one base with a pKa greater than 20;
converting the at least one quarternary ammonium salt of the benzyl ester of the depolymerized heparin to at least one salt chosen from alkali and alkaline-earth metal salts of sulphated polysaccharides of heparin;
saponifying the at least one salt; and
optionally purifying the at least one salt.

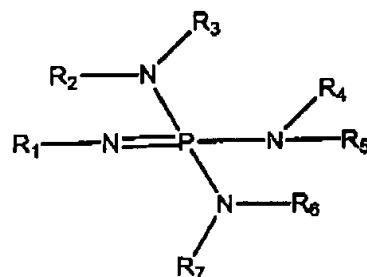
67. (Previously Presented) A method of preparing a sodium salt of sulphated polysaccharides of heparin comprising:
depolymerizing a quarternary ammonium salt of the benzyl ester of heparin in an organic medium with at least one base with a pKa greater than 20;
converting the quarternary ammonium salt of the benzyl ester of the depolymerized heparin to the sodium salt of sulphated polysaccharides of heparin;
saponifying the sodium salt; and
optionally purifying the sodium salt.

Attorney Docket No. 3806-0510-00
Application No.: 09/909,797

68. (Previously Presented) The method according to claim 67, wherein said depolymerizing step is accomplished with a single base with a pKa greater than 20.

69. (Previously Presented) The method according to claim 68, wherein said base is 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diaza-phosphorine.

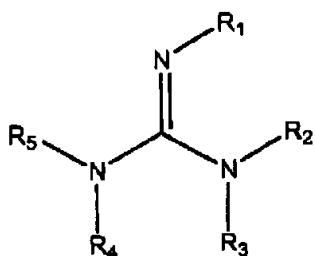
70. (Previously Presented) The method according to claim 10, in which the at least one phosphazene base is chosen from:



where R₁ to R₇ are identical or different, and are each chosen from C₁-C₆ alkyl and, further where R₃ and R₄ or R₁ and R₇, taken together with the nitrogens to which they are attached, may form a saturated ring chosen from substituted and unsubstituted six member rings.

71. (Previously Presented) The method according to claim 61, in which the at least one base of guanidine comprises:

Attorney Docket No. 3806-0510-00
Application No.: 09/909,797



where R₁ is chosen from hydrogen and alkyl, and where R₂, R₃, R₄, and R₅, which are identical or different, are each chosen from C₁-C₆ alkyl.

72. (Original) The method according to claim 71, where R₁ is hydrogen, and R₂, R₃, R₄, and R₅ are each methyl.

73. (New): A composition comprising at least one salt chosen from alkali and alkaline-earth metal salts of at least one sulphated polysaccharide of heparin, said salts of at least one sulphated polysaccharide of heparin comprising:

a mean molecular weight in the range of 1500 to 3000 daltons;

an anti-Xa activity in the range of 110 to 150 IU/mg;

an anti-IIa activity in the range of up to 10 IU/mg; and

an anti-Xa activity/anti-IIa activity ratio greater than 10:1;

wherein said salts of at least one sulphated polysaccharide of heparin have a 4,5-unsaturated glucuronic acid 2-O-sulphate unit on at least one end.

Attorney Docket No. 3806-0510-00
Application No.: 09/909,797

74. (New): A method of treating venous thrombosis in a patient in need of such treatment, comprising administering to the patient a composition as claimed in claim 73, in an amount efficacious for the treatment of venous thrombosis.

75. (New) A method of treating arterial thrombosis in a patient in need of such treatment, comprising administering to the patient a composition as claimed in claim 73, in an amount efficacious for the treatment of arterial thrombosis.

76. (New) A method of treating arterial or venous thrombosis in a patient in need of such treatment comprising the administration of a solution of a pharmaceutical composition by the subcutaneous, intramuscular, intravenous, or pulmonary route, in which a composition according to claim 73 is an active ingredient present in an amount efficacious for such treatment.

77. (New) A method of preparing a composition comprising at least one salt chosen from alkali and alkaline-earth metal salts of at least one sulphated polysaccharide of heparin as claimed in claim 1, the method comprising:

depolymerizing at least one quarternary ammonium salt of the benzyl ester of heparin in an organic medium with at least one phosphazene base;

converting the at least one quarternary ammonium salt of the benzyl ester of the depolymerized heparin to at least one salt chosen from alkali and alkaline-earth metal salts of at least one sulphated polysaccharide of heparin;

saponifying the at least one salt; and

Attorney Docket No. 3806-0510-00
Application No.: 09/909,797

optionally purifying the at least one salt.

78. (New) A method of preparing a composition comprising at least one salt chosen from alkali and alkaline-earth metal salts of at least one sulphated polysaccharide of heparin as claimed in claim 1, the method comprising:

depolymerizing at least one quarternary ammonium salt of the benzyl ester of heparin in an organic medium with sodium imidazolate;

converting the at least one quarternary ammonium salt of the benzyl ester of the depolymerized heparin to at least one salt chosen from alkali and alkaline-earth metal salts of at least one sulphated polysaccharide of heparin;

saponifying the at least one salt; and

optionally purifying the at least one salt.

79. (New) A method of preparing a composition comprising at least one salt chosen from alkali and alkaline-earth metal salts of at least one sulphated polysaccharide of heparin as claimed in claim 1, the method comprising:

depolymerizing at least one quarternary ammonium salt of the benzyl ester of heparin in an organic medium with 1,5,7 triazabicyclo-[4.4.0]-dec-5-ene;

converting the at least one quarternary ammonium salt of the benzyl ester of the depolymerized heparin to at least one salt chosen from alkali and alkaline-earth metal salts of at least one sulphated polysaccharide of heparin;

saponifying the at least one salt; and

optionally purifying the at least one salt.

Attorney Docket No. 3806-0510-00
Application No.: 09/909,797

80. (New) A method of preparing a composition comprising at least one salt chosen from alkali and alkaline-earth metal salts of at least one sulphated polysaccharide of heparin as claimed in claim 1, the method comprising:

depolymerizing at least one quarternary ammonium salt of the benzyl ester of heparin in an organic medium with at least one guanidine base;

converting the at least one quarternary ammonium salt of the benzyl ester of the depolymerized heparin to at least one salt chosen from alkali and alkaline-earth metal salts of at least one sulphated polysaccharide of heparin;

saponifying the at least one salt; and

optionally purifying the at least one salt.

81. (New) A method of preparing a composition comprising at least one salt chosen from alkali and alkaline-earth metal salts of at least one sulphated polysaccharide of heparin as claimed in claim 1, the method comprising:

depolymerizing at least one quarternary ammonium salt of the benzyl ester of heparin in an organic medium with at least one base with a pKa greater than 20;

converting the at least one quarternary ammonium salt of the benzyl ester of the depolymerized heparin to at least one salt chosen from alkali and alkaline-earth metal salts of sulphated polysaccharides of heparin;

saponifying the at least one salt; and

optionally purifying the at least one salt.